



DOCKET NO.: 18-971-0 PCT

Co/Cu

DIRECTOR OF THE UNITED STATES
PATENT AND TRADEMARK OFFICE
ALEXANDRIA, VIRGINIA 22313

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ATTORNEYS AT LAW

STEPHEN G. BAXTER
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Certificate

MAY 13 2005

of Correction

SIR:

Attached hereto for filing are the following papers:

REQUEST FOR CERTIFICATE OF CORRECTION; CERTIFICATE OF CORRECTION (IN DUPLICATE, 3 PP.); PHOTOCOPY OF ORIGINAL CLAIMS OF SPECIFICATION AS FILED 05/21/97; PHOTOCOPY OF OFFICE ACTION MAILED 08/28/97; PHOTOCOPY OF U.S. 5,376,634; PHOTOCOPY OF OFFICE ACTION MAILED 06/15/98; PHOTOCOPY OF AMENDMENT PURSUANT TO 37 C.F.R. §1.116 FILED 12/07/98; PHOTOCOPY OF PRELIMINARY AMENDMENT FILED 02/08/99

Our credit card payment form in the amount of \$100.00 is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R. §1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. §1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter
Attorney of Record
Registration No. 32

Customer Number

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**Vincent K. Shier, Ph. D.
Registration Number 50,552**

MAY 19 2005

DOCKET NO.: 18-971-0 PCT



DIRECTOR OF THE UNITED STATES
PATENT AND TRADEMARK OFFICE
ALEXANDRIA, VIRGINIA 22313

RE: Patent No.: 6,107,458

Serial No.: 08/809,723

Patentees: Hidenori OHKI et al

Issue Date: August 22, 2000

For: CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC
ACTIVITY

ATTORNEYS AT LAW

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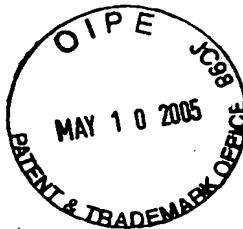
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U.S. Patent No. 6,107,458
Request for Certificate of Correction

DOCKET NO.: 18-971-0 PCT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PATENT OF:

Hidenori OHKI et al

PATENT NO.: 6,107,458

ISSUED: August 22, 2000

FOR: CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

REQUEST FOR CERTIFICATE OF CORRECTION

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ALEXANDRIA, VA 22313-

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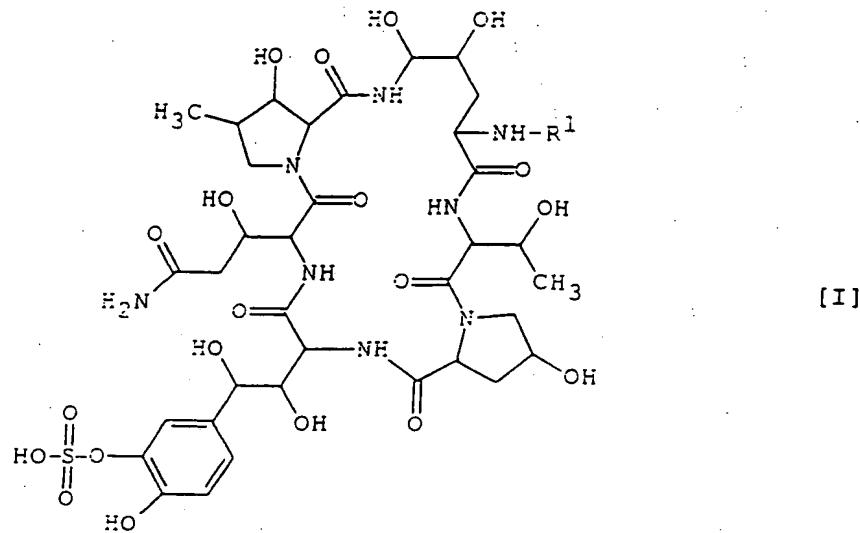
The following is a request for a Certificate of Correction in U.S. Patent Application Serial Number 08/809,723, now U.S. Patent Number 6,107,458.

REMARKS

A Certificate of Correction under 35 U.S.C. §255 is respectfully requested, in U.S. Patent Number 6,107,458 ("the '458 patent"). The facts are as follows.

The '458 patent issued from U.S. Patent Application Serial Number 08/809,723 ("the '723 application"), which was a 371 application of PCT/JP95/01983, filed on September 29, 1995. The '723 application entered the national stage in the U.S. on April 27, 1997, and the requirements of 35 U.S.C. § 371 were completed on May 21, 1997.

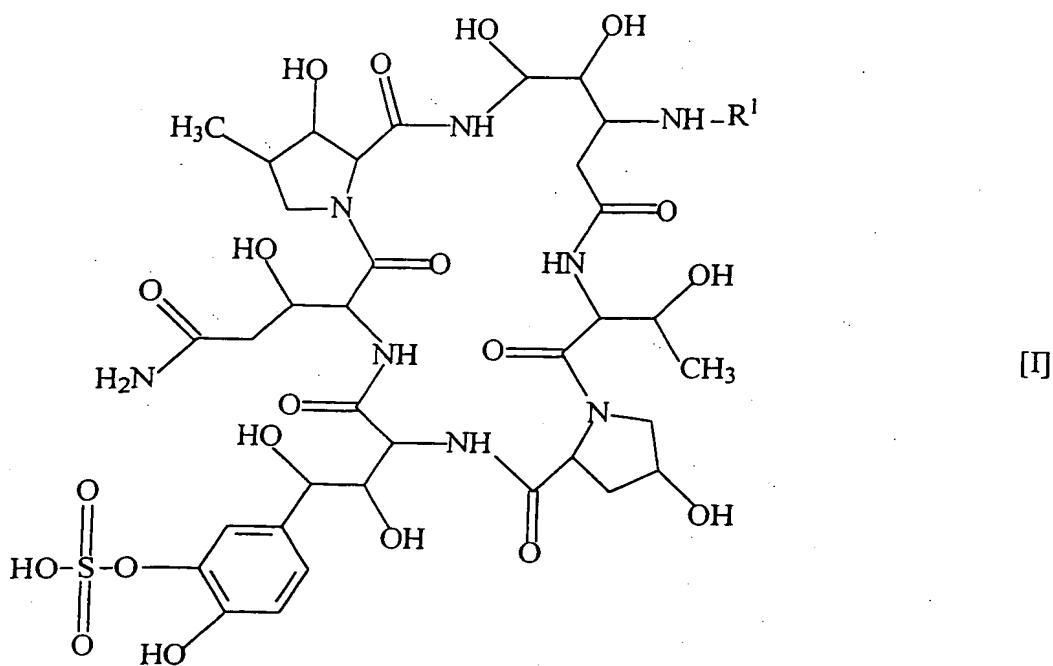
The '723 application was filed with 19 original claims, a copy of which is attached hereto at Tab 1. Notably, as shown by the formula [I] in Claim 1, the '723 application is directed toward certain cyclic hexapeptides. For convenience, formula [I] is repeated below:



It is also noted that the structure of formula [I] in originally presented Claim 1 is fully supported by the specification of both the '723 application, as originally filed, and the '458 patent, as issued. In support of this assertion, Applicants cite page 2 of the '723 application, as originally filed, and col. 1 of the '458 patent.

In the Office Action dated August 28, 1997, Claims 1-19 were rejected under 35 U.S.C. § 103(a) in view of, *inter alia*, U.S. Patent No. 5,376,634 (Iwamoto et al.). For convenience, copies of the Office Action dated August 28, 1997, and Iwamoto et al. are attached hereto at Tabs 2 and 3. In the Request for Reconsideration filed on March 2, 1998, no amendments were made to the claims other than the cancellation of Claims 17 and 18.

In the Office Action dated June 5, 1998, Claims 1-16 were finally rejected in view of Iwamoto et al. (copy attached hereto at Tab 4). In response, Applicants canceled Claims 1-16 and added new Claims 20-36 (see, copy of the Amendment Pursuant to 37 C.F.R. §1.116, filed on December 7, 1998, a copy of which is attached hereto at Tab 5). However, a typographical error was introduced into the structure for formula [I] in Claims 20, 23, 28, 29, and 30 and the structure for formula [II] in Claims 29 and 30. Specifically, the position of the attachment of the -NH-R¹ group was inadvertently moved by one position on the main ring as shown below:



Inspection of the remarks, which accompanied the Amendment, makes it clear that the shift of the position of the attachment of the $-\text{NH}-\text{R}^1$ group on the main ring was merely an inadvertent typographical error. Specifically, there is nothing in the remarks which accompanied the Amendment which would in anyway indicated that this shift in position was intentional.

In the Advisory Action dated December 21, 1998, the Examiner indicated that the amendment filed on December 7, 1998, would not be entered. Applicants then re-filed the '723 application as a CPA along with a Preliminary Amendment in which Claims 20-36 were replaced with Claims 37-41 (*see*, copy of the Preliminary Amendment, filed on February 8, 1999, a copy of which is attached hereto at Tab 6). However, the typographical error in the structure of formula [I] (and in the structure of formula [II]) which was introduced in the Amendment filed on December 7, 1998, was propagated in the Preliminary Amendment filed on February 8, 1999.

Once again, inspection of the remarks which accompanied the Preliminary Amendment filed on February 8, 1999, shows that the shift of the position of the attachment of the $-\text{NH}-\text{R}^1$ group on the main ring was merely a propagation of the inadvertent typographical error which had been previously introduced. Moreover, the fact that the Examiner then allowed the application

U.S. Patent No. 6,107,458
Request for Certificate of Correction

indicates that this typographical error simply went unnoticed and that the Examiner had intended to allow those claims with the correct structure.

In other words, the entire prosecution history points to the conclusion that the mistake in the structure of formulae [I] and [II] is simply a typographical error which went unnoticed during prosecution. Further, there is no evidence that this error was introduced in bad faith.

As stated in 35 U.S.C. § 255:

Whenever a mistake of a clerical or *typographical* nature, or of a minor character, which was not the fault of the Patent and Trademark Office, appears in a patent and a showing has been made that such mistake occurred in *good faith*, the Director may upon payment of the required fee, issue a certificate of correction, if the correction does not involve such changes in the patent as would constitute *new matter* or would require *re-examination*.

As can be seen from the facts set out above, this particular instance meets all the requirements for the issuance of a certificate of correction. Specifically, the error in the structure of formulae [I] and [II]:

- (1) is a typographical error; and
- (2) occurred in good faith.

Moreover, correction of the error in the structure of formulae [I] and [II]:

- (3) would not introduce any new matter; and
- (4) would not require re-examination.

In the Certificate of Correction filed herewith, only the correction of the structure of formulae [I] and [II] to that which was originally filed is sought. Since the specification as filed contained the correct structure, correction of the structure of formulae [I] and [II] would clearly not introduce any new matter. Further, since it is clear from the prosecution history that the error in the structure of formulae [I] and [II] simply went unnoticed during the prosecution and that both the Applicant and the Examiner both thought that the allowed claims contained the correct structure, the requested correction would just as clearly not require re-examination.

U.S. Patent No. 6,107,458
Request for Certificate of Correction

For these reasons, it is respectfully requested that the Certificate of Correction filed herewith be granted and issued.

Since all errors are the fault of the Patentee, a credit card payment form for \$100.00 is being submitted herewith. 35 U.S.C. § 255 and 37 C.F.R. § 1.323. The requested corrections are attached on Form PTO 1050.

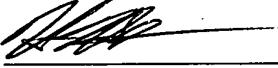
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

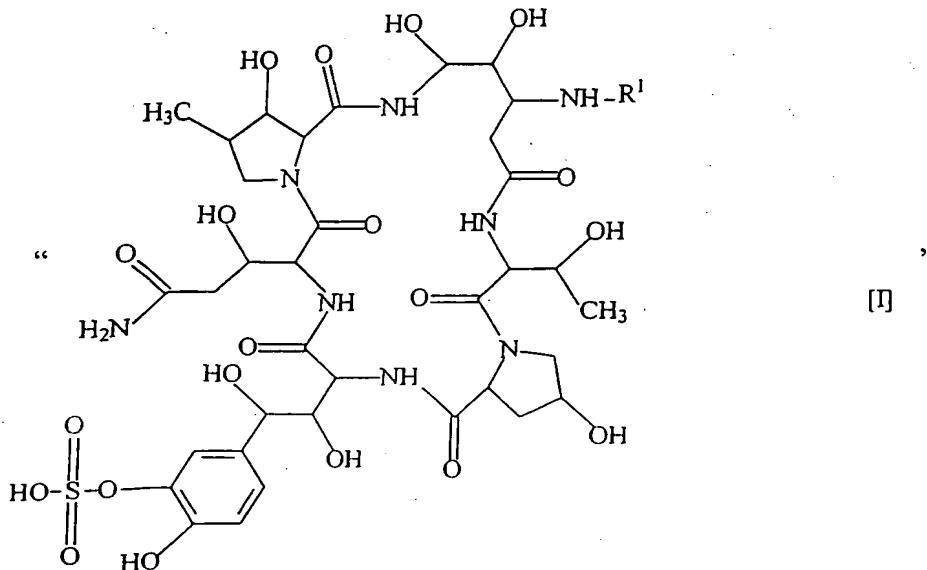
PATENT NO. : 6,170,458

DATED: August 22, 2000

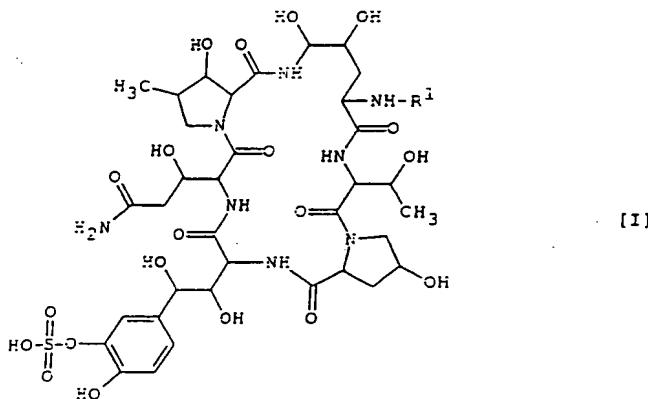
INVENTOR(S): Hidenori OHKI et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 137, lines 34-54, Claim 1, formula (I):



should read:



Mailing address of sender:

Page 1 of 3

Patent No. 6,107,458

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UNITED STATES PATENT AND TRADEMARK OFFICE
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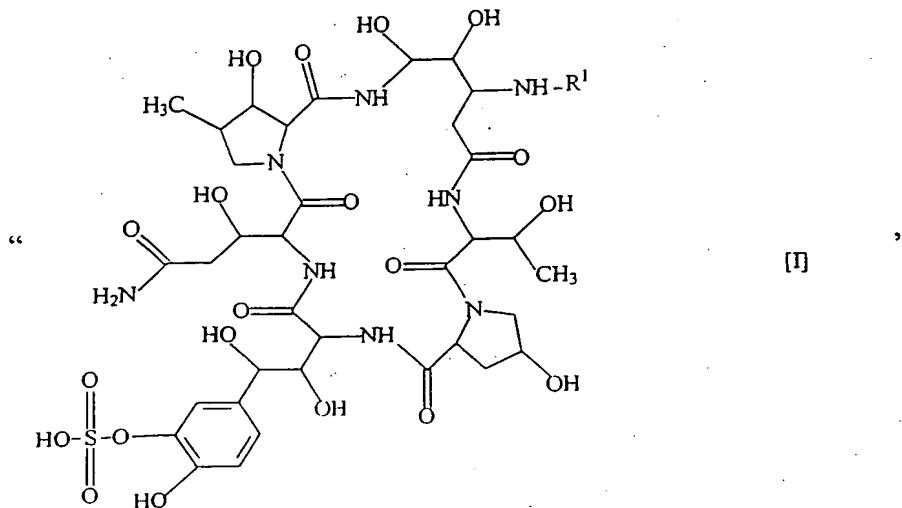
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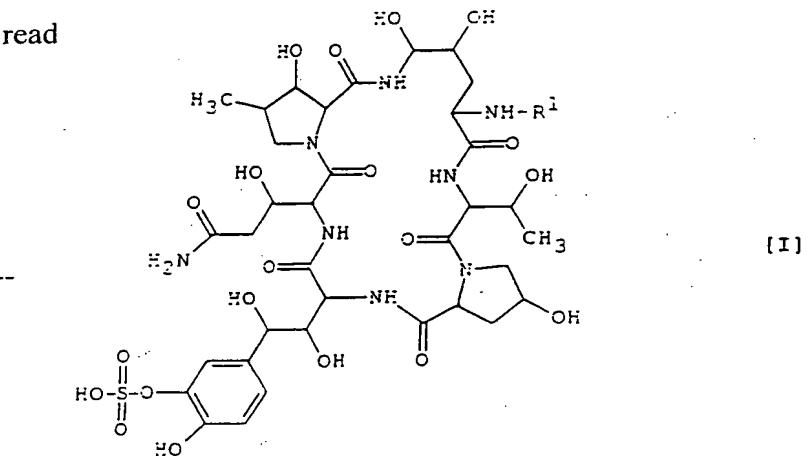
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Column 138, lines 1-23, Claim 3, formula (I):



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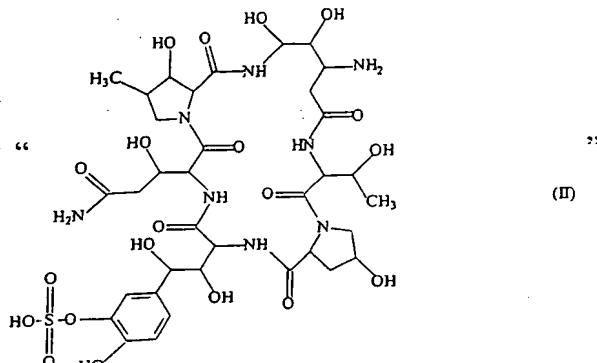
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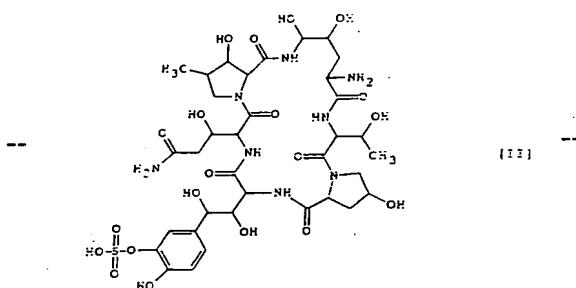
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Column 138, lines 28-49, Claim 3, formula (II):



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U.S. Patent No. 6,107,458
Request for Certificate of Correction

DOCKET NO.: 18-971-0 PCT



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PATENT NO.: 6,107,458

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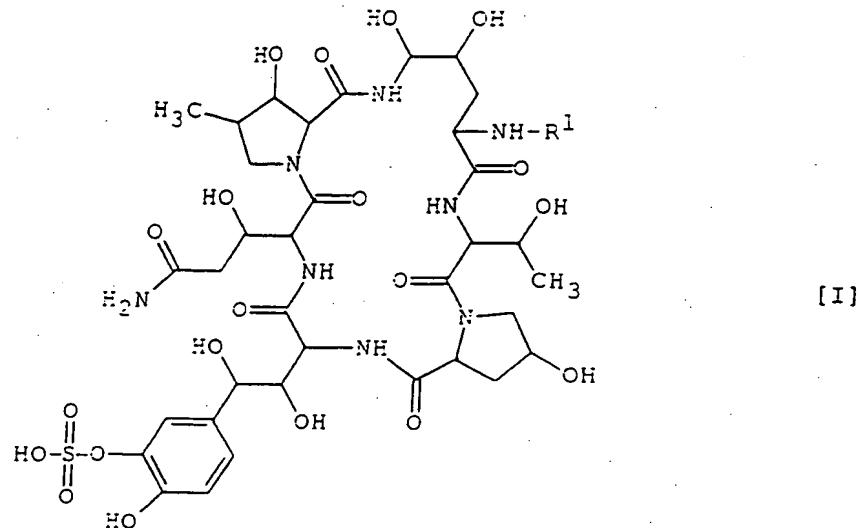
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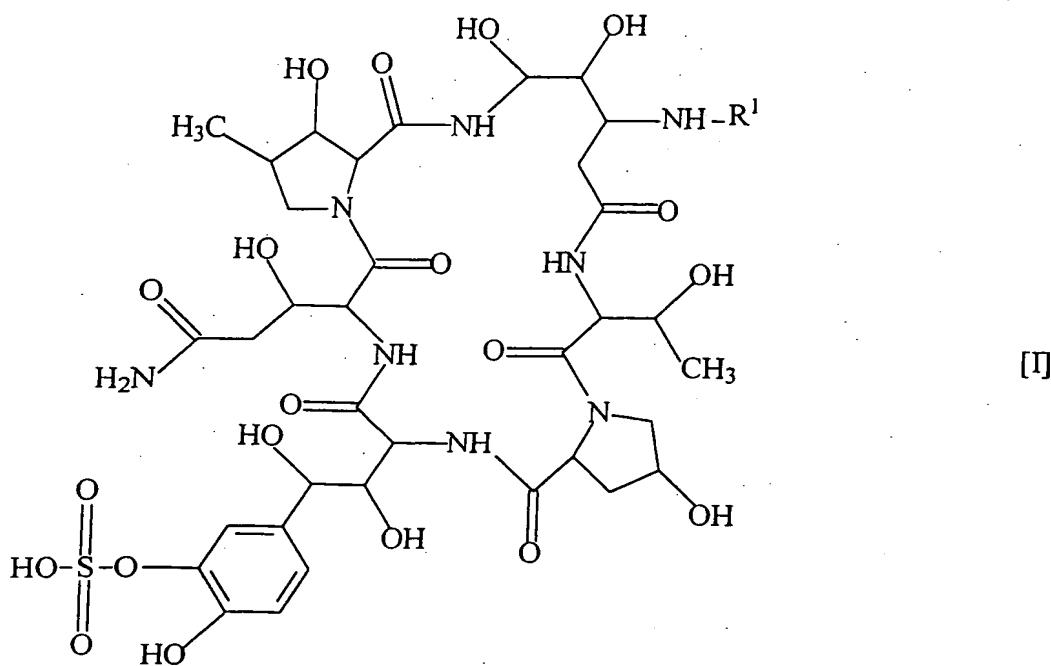
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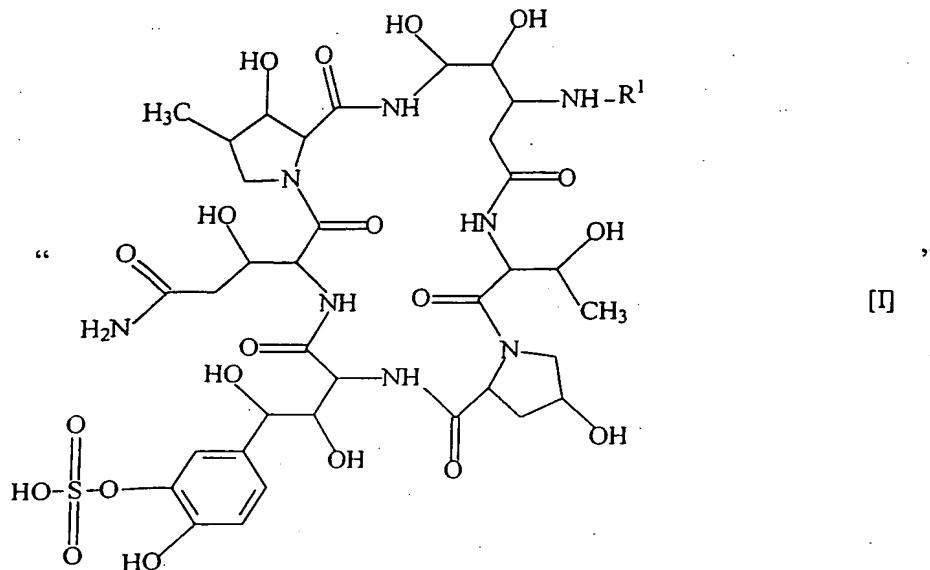
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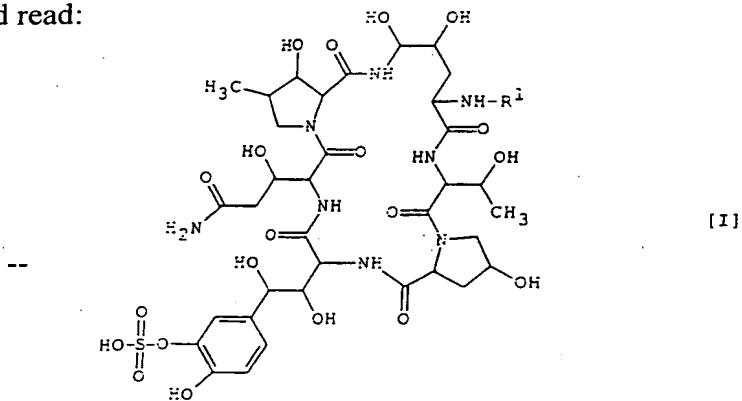
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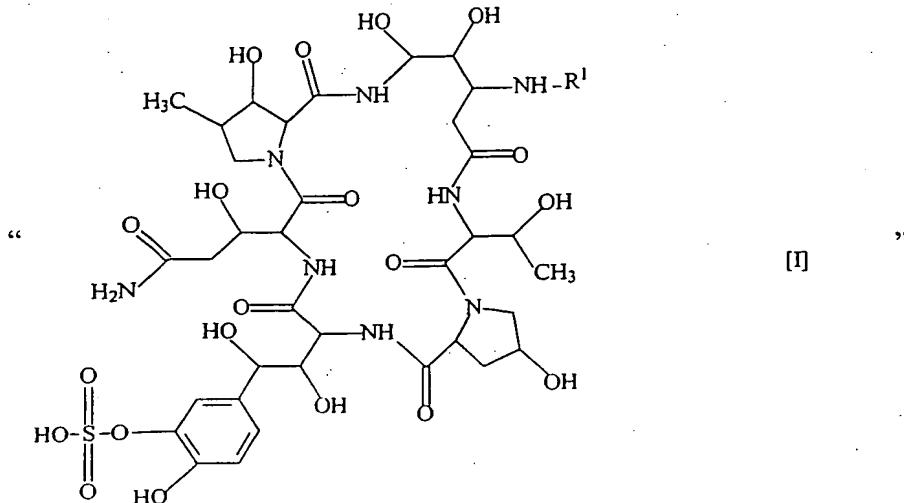
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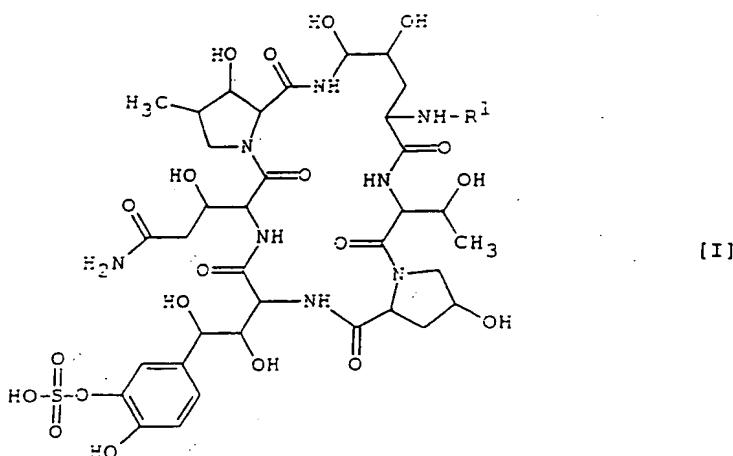
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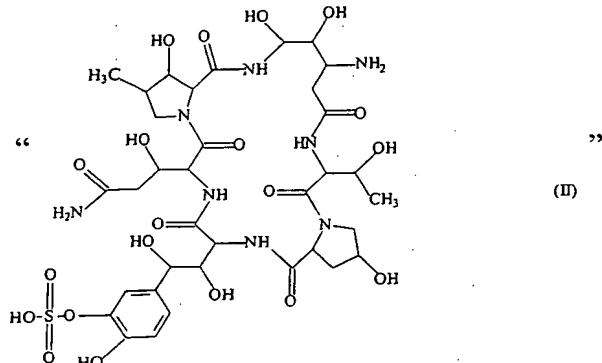
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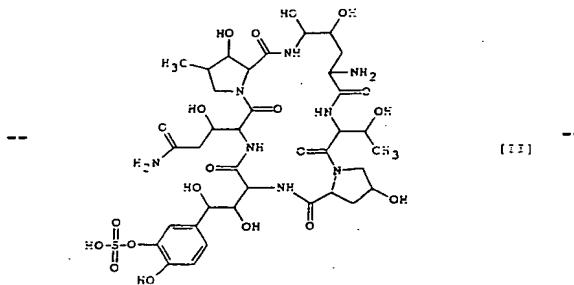
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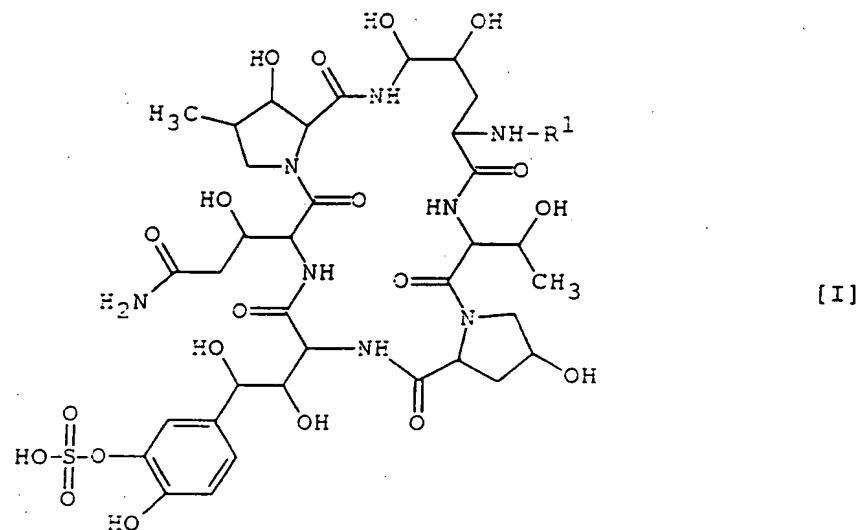


MAY 19 2005

CLAIMS

1. A polypeptide compound of the following general formula :

5



wherein R¹ is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s); lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s);
→ lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s);
→ lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s)

which may have one or more suitable
substituent(s);

→ lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with
saturated 3 to 8 membered
heteromonocyclic group containing at
least one nitrogen atom which may have
one or more suitable substituent(s);

ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenoyl which may have one or more higher alkoxy;

lower alkynoyl which may have one or more suitable substituent(s);

(C₂-C₆) alkanoyl substituted with naphthyl having higher alkoxy;

ar(C₂-C₆) alkanoyl substituted with aryl having one or more suitable substituent(s), in which ar(C₂-C₆)- alkanoyl may have one or more suitable substituent(s).

aryloyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which arroyl may have one or more suitable substituent(s);

aryloxy substituted with aryl having heterocyclic(higer)alkoxy, in which heterocyclic group may have one or more suitable substituent(s);

arcyl substituted with aryl having lower alkoxy(lower)alkoxy;

5 aroyl substituted with aryl having lower alkenyl(lower)alkoxy;

arcyl substituted with 2 lower alkoxy;

arcyl substituted with aryl having lower alkyl;

10 aroyl substituted with aryl having higher alkyl;

aryloxy(lower)alkanoyl which may have one or more suitable substituent(s);

15 ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s);

arylamino(lower)alkanoyl which may have one or more suitable substituent(s);

20 lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy;

lower alkoxy(lower)alkanoyl, in which higher alkanoyl may have one or more suitable substituent(s);

25 aroyl substituted with aryl having heterocyclicoxy, in which heterocyclicoxy may have one or more suitable substituent(s);

30 aroyl substituted with cyclo(lower)alkyl having lower alkyl; indolylcarbonyl having higher alkyl; naphthoyl having lower alkyl; naphthoyl having higher alkyl; naphthoyl having lower alkoxy(lower)alkoxy;

5 aroyl substituted with aryl having lower alkoxy(lower)alkoxy(higer)-alkoxy;

10 aroyl substituted with aryl having lower alkoxy(lower)alkoxy;

15 aroyl substituted with aryl which has aryl having lower alkoxy;

20 aroyl substituted with aryl which has aryl having lower alkoxy(lower)alkoxy;

25 aroyl substituted with aryl having heterocyclicoxy(higer)alkoxy;

30 aroyl substituted with aryl having aryloxy(lower)alkoxy;

35 aroyl substituted with aryl having heterocycliccarbonyl(higer)alkoxy;

40 lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy;

45 lower alkanoyl substituted with furyl which has aryl substituted with aryl having lower alkoxy;

50 lower alkanoyl substituted with triazolyl which has oxo and aryl having higher alkyl;

55 higher alkanoyl having hydroxy;

60 higher alkanoyl having ar(lower)alkyl and hydroxy;

65 3-methyl-tridecenoyl; or

70 (C₂-C₆)alkanoyl substituted with aryl having higher alkoxy, in which (C₂-C₆)-alkanoyl may have amino or protected amino, and

75 a pharmaceutically acceptable salt thereof.

35 2. A compound of claim 1, wherein

R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having higher alkoxy, phenyl substituted with phenyl having lower alkoxy, 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having lower alkoxy(lower)alkoxy, 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having lower alkoxy, and oxo;

lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline having higher alkoxy and lower alkoxy carbonyl;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy,

naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have higher alkoxy, and oxo;

10 lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

20 lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atoms which may have 1 to 3 substituent(s) selected from the group containing of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo; or

30 lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3

substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

10

3. A compound of claim 1, wherein
R¹ is ar(lower)alkenoyl substituted with aryl which
may have 1 to 3 substituent(s) selected from the
group consisting of lower alkoxy, higher alkoxy,
lower alkyl, higher alkyl, higher
alkoxy(lower)alkyl, phenyl having lower alkoxy,
phenyl having higher alkoxy, naphthyl having lower
alkoxy, naphthyl having higher alkoxy, phenyl
having lower alkyl, phenyl having higher alkyl,
naphthoyl having higher alkoxy, phenyl substituted
with phenyl having lower alkyl, lower
alkoxy(lower)alkyl, halo(lower)alkoxy, lower
alkenyloxy, halo(higher)alkoxy, lower
alkoxy(higher)alkoxy, and oxo;
naphthyl(lower)alkenoyl which may have 1 to 3
higher alkoxy;
lower alkynoyl which may have 1 to 3
substituent(s) selected from the group consisting
of lower alkoxy, higher alkoxy, lower alkyl,
higher alkyl, higher alkoxy(lower)alkyl, phenyl
having lower alkoxy, phenyl having higher alkoxy,
naphthyl having lower alkoxy, naphthyl having
higher alkoxy, phenyl having lower alkyl, phenyl
having higher alkyl, naphthoyl having higher
alkoxy, phenyl substituted with phenyl having

lower alkyl, and oxo;

5 ar(C₂-C₆) alkanoyl substituted with aryl having 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, phenyl having lower alkoxy(lower)alkoxy, and oxo, in which ar(C₂-C₆)-alkanoyl may have hydroxy, oxo, protected amino or amino; or

10 (C₂-C₆) alkanoyl substituted with naphthyl having higher alkoxy.

4. A compound of claim 1, wherein

20 R¹ is aroyl substituted with heterocyclic group which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, phenyl having lower alkoxy(lower)alkoxy, phenyl having higher alkenyloxy, heterocyclic group substituted with phenyl having lower alkoxy, heterocyclic group, cyclo(lower)alkyl having phenyl, phenyl having cyclo(lower)alkyl, phenyl substituted with heterocyclic group having lower alkyl and oxo, cyclo(lower)alkyl having lower alkyl, phenyl

substituted with phenyl having lower alkoxy, phenyl having heterocyclic group and oxo, in which aroyl may have halogen;

5 aroyl substituted with aryl having heterocyclic(higher)alkoxy, in which heterocyclic group may have lower alkyl;

10 aroyl substituted with aryl having lower alkoxy(higher)alkoxy;

15 aroyl substituted with aryl having lower alkenyl(lower)alkoxy;

15 aroyl substituted with 2 lower alkoxy;

20 aroyl substituted with aryl having lower alkyl; or

25 aroyl substituted with aryl having higher alkyl.

15

5. A compound of claim 1, wherein

20 R^1 is aryloxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl,

25 higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

30

35 ar(lower)alkoxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl

35

having lower alkyl, and oxo; or

aryl amino(lower) alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower) alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

6. A compound of claim 1, wherein
R¹ is lower alkanoyl substituted with pyrazolyl which
has lower alkyl and aryl having higher alkoxy;
lower alkoxy(higer) alkanoyl, in which higher
alkanoyl may have amino or protected amino;
aroyl substituted with aryl having
heterocyclicoxy, in which heterocyclicoxy may have
phenyl;
aroyl substituted with cyclo(lower)alkyl having
lower alkyl;
indolylcarbonyl having higher alkyl;
naphthoyl having lower alkyl;
naphthoyl having higher alkyl;
naphthoyl having lower alkoxy(higer) alkoxy;
aroyl substituted with aryl having lower
alkoxy(lower)alkoxy(higer)alkoxy;
aroyl substituted with aryl having lower
alkoxy(lower)alkoxy;
aroyl substituted with aryl which has phenyl
having lower alkoxy;
aroyl substituted with aryl which has phenyl
having lower alkoxy(lower)alkoxy;
aroyl substituted with aryl having

heterocyclicoxy(higer)alkoxy;
5 aroyl substituted with aryl having
phenoxy(lower)alkoxy;
aroyl substituted with aryl having
heterocycliccarbonyl(higer)alkoxy;
lower alkanoyl substituted with oxazolyl which
has aryl having higher alkoxy;
lower alkanoyl substituted with furyl which has
aryl substituted with phenyl having lower alkoxy;
10 lower alkanoyl substituted with triazolyl which
has oxo and phenyl having higher alkyl;
higher alkanoyl having hydroxy;
higher alkanoyl having benzyl and hydroxy;
3-methyl-tridecenoyl; or
15 (C₂-C₆) alkanoyl substituted with aryl having
higher alkoxy, in which (C₂-C₆) alkanoyl may have
amino or protected amino.

7. A compound of claim 2, wherein
20 R¹ is lower alkanoyl substituted with pyridyl or
pyridazinyl, each of which may have 1 to 3
substituent(s) selected from the group consisting
of higher alkoxy, higher alkoxy(lower)alkyl,
phenyl having higher alkoxy, phenyl substituted
25 with phenyl having lower alkoxy, piperazinyl
substituted with phenyl having higher alkoxy,
piperazinyl substituted with phenyl having lower
alkoxy(higer)alkoxy, and piperazinyl substituted
with phenyl having lower alkoxy;
lower alkanoyl substituted with 1,2,3,4-
30 tetrahydroisoquinoline having higher alkoxy and
lower alkoxy carbonyl;
lower alkanoyl substituted with coumarin which
may have 1 to 3 substituent(s) selected from the
group consisting of higher alkoxy, and oxo;
35

lower alkanoyl substituted with benzothiophenyl which may have 1 to 3 higher alkoxy;

5 lower alkanoyl substituted with benzo[b]furanyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkoxy and lower alkyl;

10 lower alkanoyl substituted with benzooxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl substituted with phenyl having lower alkyl, and pyridyl having higher alkoxy;

15 lower alkanoyl substituted with benzimidazolyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, and phenyl having lower alkoxy; or

20 lower alkanoyl substituted with piperidyl or piperazinyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having higher alkoxy, and naphthoyl having higher alkoxy.

8. A compound of claim 3, wherein

25 R^1 is phenyl(lower)alkenoyl substituted with phenyl

which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, lower alkyl, higher alkyl, lower alkoxy(lower)alkyl, halo(lower)alkoxy, lower alkenyloxy, halo(higer)alkoxy, and lower alkoxy(higer)alkoxy;

30 naphthyl(lower)alkenoyl which may have 1 to 3 higher alkoxy;

lower alkynoyl which may have 1 to 3 substituent(s) selected from the group consisting of naphthyl having higher alkoxy, and phenyl

substituted with phenyl having lower alkyl;
phenyl(C₂-C₆) alkanoyl substituted with phenyl
which has 1 to 3 substituent(s) selected from the
group consisting of lower alkoxy, higher alkoxy,
lower alkyl, higher alkyl, and phenyl having lower
alkoxy(lower) alkyl,
in which phenyl(C₂-C₆) alkanoyl may have hydroxy,
oxo, protected amino or amino; or
(C₂-C₆) alkanoyl substituted with naphthyl having
higher alkoxy.

9. A compound of claim 4, wherein

R¹ is benzoyl substituted with saturated 6-membered
heteromonocyclic group containing at least one
nitrogen atom which may have 1 to 3 substituent(s)
selected from the group consisting of phenyl
having lower alkoxy, phenyl having higher alkoxy,
phenyl having lower alkyl, phenyl having lower
alkoxy(higher) alkoxy, phenyl having higher
alkenyloxy, piperidyl substituted with phenyl
having lower alkoxy, piperidyl, cyclo(lower)alkyl
having phenyl, phenyl having cyclo(lower)alkyl,
and phenyl substituted with triazolyl having oxo
and lower alkyl,

in which benzoyl may have halogen;
benzoyl substituted with unsaturated 5-membered
heteromonocyclic group containing 1 to 2 oxygen
atom(s) and 1 to 3 nitrogen atom(s) which may have
1 to 3 substituent(s) selected from the group
consisting of higher alkyl, phenyl having lower
alkoxy, phenyl having higher alkoxy, phenyl having
lower alkoxy(higher) alkoxy, and phenyl substituted
with phenyl having lower alkoxy;

benzoyl substituted with 5 or 6-membered
heteromonocyclic group containing 1 or 2 nitrogen

atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl and phenyl having lower alkoxy;

benzoyl substituted with phenyl having higher
alkoxy substituted with saturated 6-membered
heteromonocyclic group containing 1 to 2 oxygen
atom(s) and 1 to 3 nitrogen atom(s) which may have
lower alkyl;

benzoyl substituted with phenyl having lower
alkoxy(higer)alkoxy;

benzoyl substituted with phenyl having lower
alkenyl(lower)alkoxy;

benzoyl substituted with 2 lower alkoxy;

benzoyl substituted with phenyl having lower alkyl; or

30 benzoyl substituted with phenyl having higher
alkyl.

10. A compound of claim 5, wherein

R^1 is phenoxy(lower)alkanoyl which may have 1 to 3 higher alkoxy;

35 higher alkoxy;

phenyl(lower)alkoxy(lower)alkanoyl which may have 1 to 3 higher alkoxy; or phenylamino(lower)alkanoyl which may have 1 to 3 higher alkoxy.

5

11. A compound of claim 1, wherein R¹ is benzoyl substituted with piperazinyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkyl, phenyl having lower alkoxy(lower)alkoxy, phenyl having higher alkenyloxy, piperidyl substituted with phenyl having lower alkoxy, cyclo(lower)alkyl having phenyl, phenyl having cyclo(lower)alkyl, and phenyl substituted with triazolyl having oxo and lower alkyl,
15 in which benzoyl may have halogen;
benzoyl substituted with isoxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy(lower)alkoxy, and phenyl substituted with phenyl having lower alkoxy;
20 benzoyl substituted with phenyl having lower alkoxy(lower)alkoxy;
benzoyl substituted with phenyl having lower alkyl;
25 benzoyl substituted with phenyl having higher alkyl;
phenyl(lower)alkenoyl substituted with phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, lower alkyl, higher alkyl, lower alkoxy(lower)alkyl, halo(lower)alkoxy, lower alkenyloxy,
30 halo(lower)alkoxy and lower alkoxy(lower)alkoxy;

35

benzoyl substituted with thiadiazolyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, cyclo(lower)alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having cyclo(lower)alkyl, phenyl having piperidyl, and phenyl having lower alkoxy(higer)alkoxy; or

benzoyl substituted with oxadiazolyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy(higer)alkoxy, higher alkyl and phenyl substituted with phenyl having lower alkoxy.

15

12. A compound of claim 11, wherein

R^1 is benzoyl substituted with phenyl having lower alkoxy(higer)alkoxy; or

benzoyl substituted with phenyl having lower alkyl.

20

13. A compound of claim 11, wherein

R^1 is benzoyl substituted with piperazinyl which may have phenyl having lower alkoxy;

25

benzoyl substituted with isoxazolyl which may have phenyl having lower alkoxy;

benzoyl substituted with thiadiazolyl which may have phenyl having lower alkoxy(higer)alkoxy; or

30

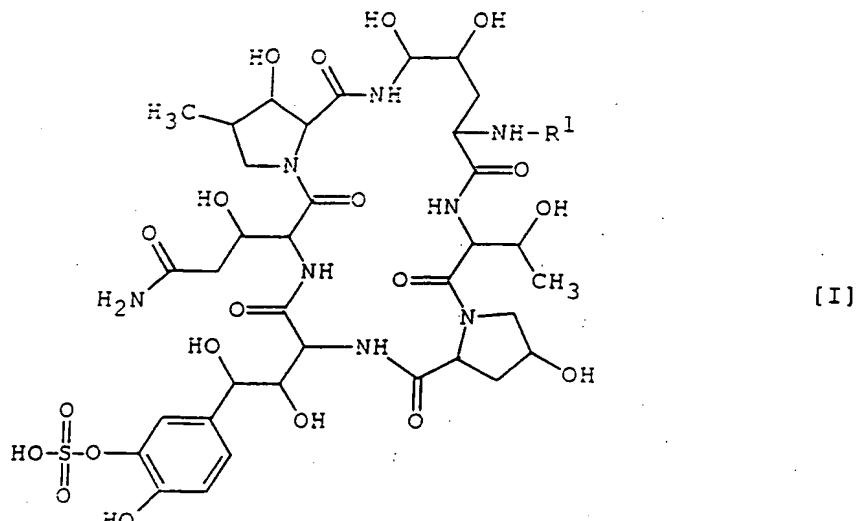
benzoyl substituted with oxadiazolyl which may have phenyl having lower alkoxy.

14. A compound of claim 11, wherein

R^1 is phenyl(lower)alkenoyl substituted with phenyl which may have lower alkoxy.

35

15. A process for the preparation of a polypeptide compound of the formula [I] :



wherein

R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s):

lower alkanoyl substituted with 1,2,3,4-tetrahydro-isouquinoline having higher alkoxy:

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s):

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

5 ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenyl which may have one or more higher alkoxy;

10 lower alkynoyl which may have one or more suitable substituent(s);

(C₂-C₆) alkanoyl substituted with naphthyl having higher alkoxy;

15 ar(C₂-C₆) alkanoyl substituted with aryl having one or more suitable substituent(s), in which ar(C₂-C₆) alkanoyl may have one or more suitable substituent(s);

20 aroyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s);

25 aroyl substituted with aryl having heterocyclic(higher)alkoxy, in which heterocyclic group may have one or more suitable substituent(s);

30 aroyl substituted with aryl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower aikenyyl(lower)alkoxy;

aroyl substituted with 2 lower alkoxy;

aroyl substituted with aryl having lower alkyl;

aryloxy(lower) alkanoyl which may have one or more suitable substituent(s);

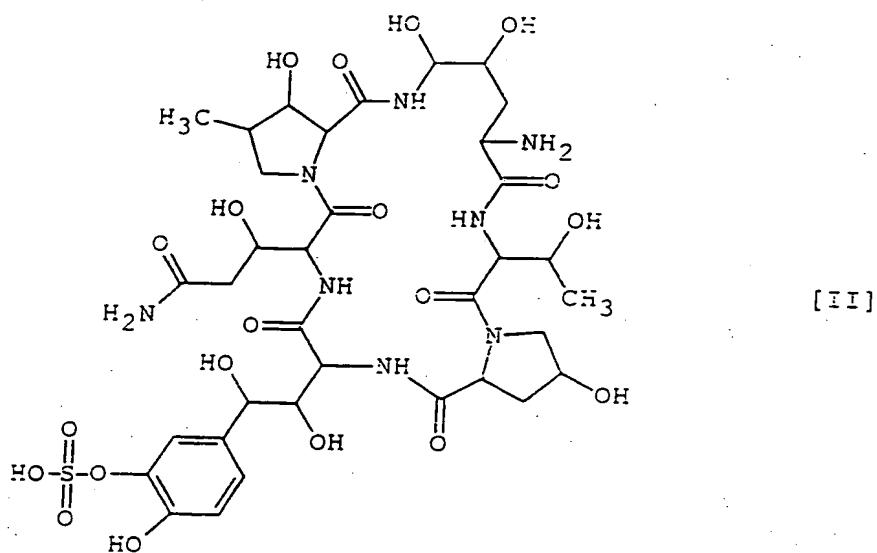
35 ar(lower)alkoxy(lower) alkanoyl which may have one or more suitable substituent(s);

arylamino(lower) alkanoyl which may have one or
more suitable substituent(s);
lower alkanoyl substituted with pyrazolyl which
has lower alkyl and aryl having higher alkoxy;
5 lower alkoxy(higer) alkanoyl, in which higher
alkanoyl may have one or more suitable
substituent(s);
10 aroyl substituted with aryl having
heterocyclicoxy, in which heterocyclicoxy may have
one or more suitable substituent(s);
15 aroyl substituted with cyclo(lower)alkyl having
lower alkyl;
indolylcarbonyl having higher alkyl;
naphthoyl having lower alkyl;
naphthoyl having higher alkyl;
naphthoyl having lower alkoxy(higer) alkoxy;
20 aroyl substituted with aryl having lower
alkoxy(lower) alkoxy;
aroyl substituted with aryl having lower
alkoxy(lower) alkoxy;
aroyl substituted with aryl which has aryl
having lower alkoxy;
aroyl substituted with aryl which has aryl
having lower alkoxy(lower) alkoxy;
25 aroyl substituted with aryl having
heterocyclicoxy(higer) alkoxy;
aroyl substituted with aryl having
aryloxy(lower) alkoxy;
aroyl substituted with aryl having
30 heterocycliccarbonyl(higer) alkoxy;
lower alkanoyl substituted with oxazolyl which
has aryl having higher alkoxy;
lower alkanoyl substituted with furyl which has
aryl substituted with aryl having lower alkoxy;
35 lower alkanoyl substituted with triazolyl which

has oxo and aryl having higher alkyl;
higher alkanoyl having hydroxy;
higher alkanoyl having ar(lower)alkyl and
hydroxy;

5 3-methyl-tridecenoyl; or
(C₂-C₆) alkanoyl substituted with aryl having
higher alkoxy, in which (C₂-C₆) alkanoyl may have
amino or protected amino, and
a pharmaceutically acceptable salt thereof,
10 which comprises

15 1) reacting a compound of the formula :

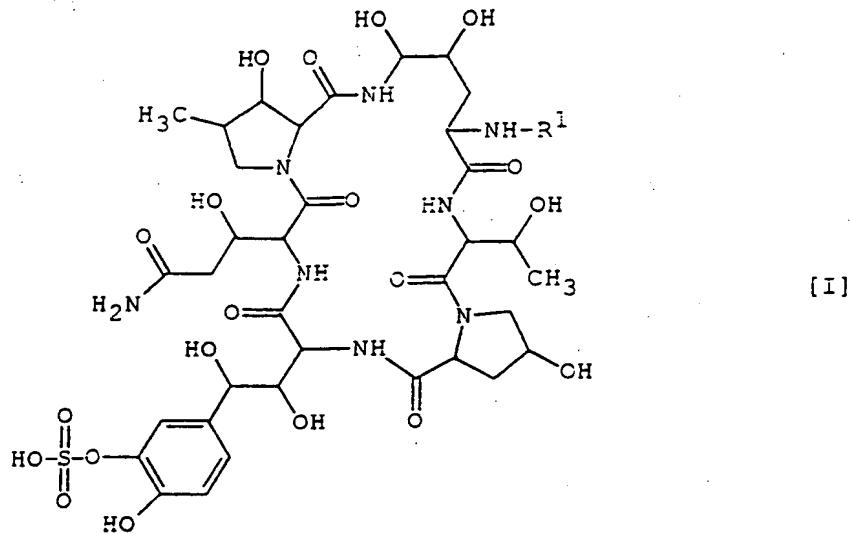


30 or its reactive derivative at the amino group or a salt thereof, with a compound of the formula :



[III]

35 wherein R¹ is defined above,
or its reactive derivative at the carboxy group or a
salt thereof, to give a compound [I] of the formula :



wherein R^1 is defined above,
or a salt thereof.

5

16. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

10

17. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a medicament.

15

18. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

20

19. A method for the prophylactic and/or the therapeutic treatment of infectious diseases caused by pathogenic microorganisms which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

THN
8-29-97

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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/809,729 05/21/97 OHKI

H 18-971-0-PCT

EXAMINER

18M1/0828

OBLON, SPIVAK, McCLELLAND,
MAIER AND NEUSTADT
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON VA 22202

ART UNIT PAPER NUMBER

5

1811

DATE MAILED: 08/28/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

RD 11-28-97

This application has been examined Responsive to communication filed on _____ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892.
2. Notice of Draftsman's Patent Drawing Review, PTO-948.
3. Notice of Art Cited by Applicant, PTO-1449.
4. Notice of Informal Patent Application, PTO-152.
5. Information on How to Effect Drawing Changes, PTO-1474.
6.

Part II SUMMARY OF ACTION

1. Claims 1-17 are pending in the application.
2. Of the above, claims _____ are withdrawn from consideration.
3. Claims _____ are allowed.
4. Claims 1-17 are rejected.
5. Claims _____ are objected to.
6. Claims _____ are subject to restriction or election requirement.
7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. Formal drawings are required in response to this Office action.
9. The corrected or substitute drawings have been received on _____ Under 37 C.F.R. 1.84 these drawings are acceptable; not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been approved by the examiner; disapproved by the examiner (see explanation).
11. The proposed drawing correction, filed _____, has been approved; disapproved (see explanation).
12. Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. _____; filed on _____.
13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. Other

RECEIVED

AUG 29 1997

EXAMINER'S ACTION

OBLON, SPIVAK, McCLELLAND
MAIER & NEUSTADT, P.C.

Art Unit: 1811

1. Claims 17-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 provides for the use of a compound or a salt thereof as a medicament, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 17 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966)

Claim 18 is a duplicate of claim 1 because claim 18 has no further structural limitation that would distinguish the compounds recited in claim 18 from those recited in claim 1.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Art Unit: 1811

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toshiro et al (EPA 0462531) or Toshio et al (USP 5,376634).

The present invention relates to compounds that have the generally formula set forth on pages 2-5 of the specification. The instant compounds have antimicrobial activity. Additionally, the invention also relates to a process of making said compounds.

Toshiro et al (EPA 0462531) teaches antimicrobial compounds which read on the compound of the present invention, especially when R1 is acyl, R2 is hydroxyl, and R3 is hydrosulfonyloxy, and R4 is carbamoyl provided that R1 is not palmitoyl. The compounds of the present invention fall with the scope of the invention taught by Toshiro et al. Therefore it would be obvious to one of ordinary skill in the art to preferentially selective the appropriate radicals needed to prepare the compounds of the present invention. Furthermore it would be within the skill of the art and therefore obvious to use the process taught by Toshiro et al to prepare the peptides of the instant invention, wherein the compounds have antimicrobial activity.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

Art Unit: 1811

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 5,374634. Although the conflicting claims are not identical, they are not patentably distinct from each other because the invention are co-extensive. Essentially, the present invention relates to compounds, pharmaceutical compositions, and a methods of making compounds set forth on pages 2-5 of the specification. The compounds of the instant invention fall within the scope of the invention taught by Toshiro et al; therefore it is within the skill of the art to preferentially select the appropriate radicals for preparing the compounds of the invention, wherein the compounds have antimicrobial activity.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

Art Unit: 1811

this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applicants Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Marshall whose telephone number is (703) 308-1030.

Sgm
August 26, 1997

CJTs
CECILIA J. TSANG
SUPERVISORY PATENT EXAMINER
GROUP 1800

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821-1.825 for the following reason(s):

1. This application clearly fails to comply with the requirements of 37 CFR 1.825. Applicant's attention is directed to these regulations, published at 1114 C May 15, 1990 and at 55 FR 18230, May 1, 1990.

2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

7.

Other: _____

Applicant must provide:

An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123

For CRF submission help, call (703) 308-4212

For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.

FORM PTO-892 (REV. 2-92)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO. 08/809723	GROUP ART. UNIT 1811	ATTACHMENT TO PAPER NUMBER 5
NOTICE OF REFERENCES CITED		APPLICANT(S) OHKI ET AL		MAY 10 2005

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
A	5 3 7 6 6 3 4	12/27/94	Iwamoto et al	530	317	
B						
C						
D						
E						
F						
G						
H						
I						
J						
K						

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PP. SPEC.
L	0 4 6 2 5 3 1	12/27/91	EP					
M								
N								
O								
P								
Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

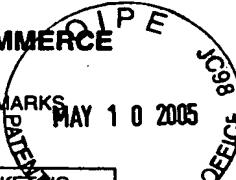
R	
S	
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EXAMINER	DATE	
SANDRA MARSHALL	8-26-01	

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

**UNITED STATES DEPARTMENT OF COMMERCE****Patent and Trademark Office**Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

MAY 10 2005

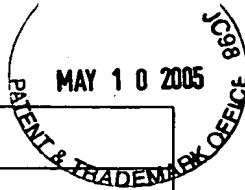
THN
6-8-98

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKER NO.
08/809,723	05/21/97	GRANT	18-971-0-PC1
08/809,723		HM11/0605	
OBLON, SPIVAK MCCLELLAND MAIER AND NEUSTADT FOURTH FLOOR 1755 JEFFERSON DAVIS HIGHWAY ARLINGTON VA 22202			EXAMINER MARSHALL, C.
			ART UNIT 1654
			PAPER NUMBER

DATE MAILED: 06/05/98

RD 9-5-98.
NA 10-5-98 (1st)**Please find below and/or attached an Office communication concerning this application or proceeding.****Commissioner of Patents and Trademarks****RECEIVED**
JUN 08 1998OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

MAY 10 2005



Office Action Summary

Application No.	08 809723	Applicant(s)	OHKI et al
Examiner	Marshall	Group Art Unit	1654

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

Responsive to communication(s) filed on _____.

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

Claim(s) 1-16 and 19 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 1-16 and 19 is/are rejected.

Claim(s) _____ is/are objected to.

Claim(s) _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The proposed drawing correction, filed on _____ is approved disapproved.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Attachment(s)

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ Interview Summary, PTO-413

Notice of References Cited, PTO-892 Notice of Informal Patent Application, PTO-152

Notice of Draftsperson's Patent Drawing Review, PTO-948 Other _____

Office Action Summary

Art Unit: 1811

Claims 1-16 and 19 are pending in the case, and claims 17-18 have been cancel.

The rejection of claims 1-16 and 19 under 103(a) as being unpatentable over Toshiro et al (EPA0462531) or Toshiro et al (Us Patent 5, 376634) has been maintained as set forth in the office action mailed August 28, 1997 on pages 2-3 . Additionally, the rejection of claims 1-16 and 19 under the judicially created doctrine of obviousness-typed double patenting has been maintained.

Applicant's arguments filed March 2, 1998 have been fully considered but they are not persuasive.

Applicants agree with the examiner that the compounds of instant invention falls within the scope of the invention as taught by Toshiro et al. However, applicants' argue that the examiner provides no reason as to why one of skill in the art would be motivated from the teaching of the reference, to pick the specific acyl group of the instant invention.

Although the patent of Toshiro et al teaches R1 is acyl, Toshiro et al also define acyl groups as being lower alkanoyl, e.g. formyl , acetyl , propionyl, butyl... which may be substituted....(see Toshiro et al, col. 6, lines 30-68), , of which the preferred acyl is lower alkanoyl, including heterocyclic lower alkanoyl (see col.8, lines 14-68). These compounds read essentially on the compounds of applicants(see spec. 2-20) Therefore the compounds of the instant invention largely overlap the compounds of the reference, and one of ordinary skill in the art at the time that the invention was made would have been motivated to preferentially select the desired acyl group to obtain compounds of the instant invention that possess anitmicrobial

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activity, especially anti fungal activity. Applicants' situation is not an *In re Baird* situation. In *In re Baird*, one would have to pick and choose from various radicals to come up with the claimed invention. In this invention, ~~their~~ is a large overlap in the compounds.

The Declaration submitted by applicants has been carefully considered, however; the small number of peptides tested is not commensurate in scope with the protection sought. Therefore the rejections are maintained. However, the specific compounds tested and showed unexpected results are allowable if presented.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Marshall whose telephone number is (703) 308-1030.

Art Unit: 1811

sgm
June 4, 1998

① Tsang

CECILIA J. TSANG
SUPERVISORY PATENT EXAMINER
GROUP 1800

DOCKET NO: 18-971-0 PCT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

HIDENORI OHKI, ET AL. : GROUP ART UNIT: 1654

SERIAL NO: 08/809,723 : EXAMINER: MARSHALL, S.

FILED: MAY 21, 1997 :

FOR: CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

AMENDMENT PURSUANT TO 37 C.F.R. §1.116

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

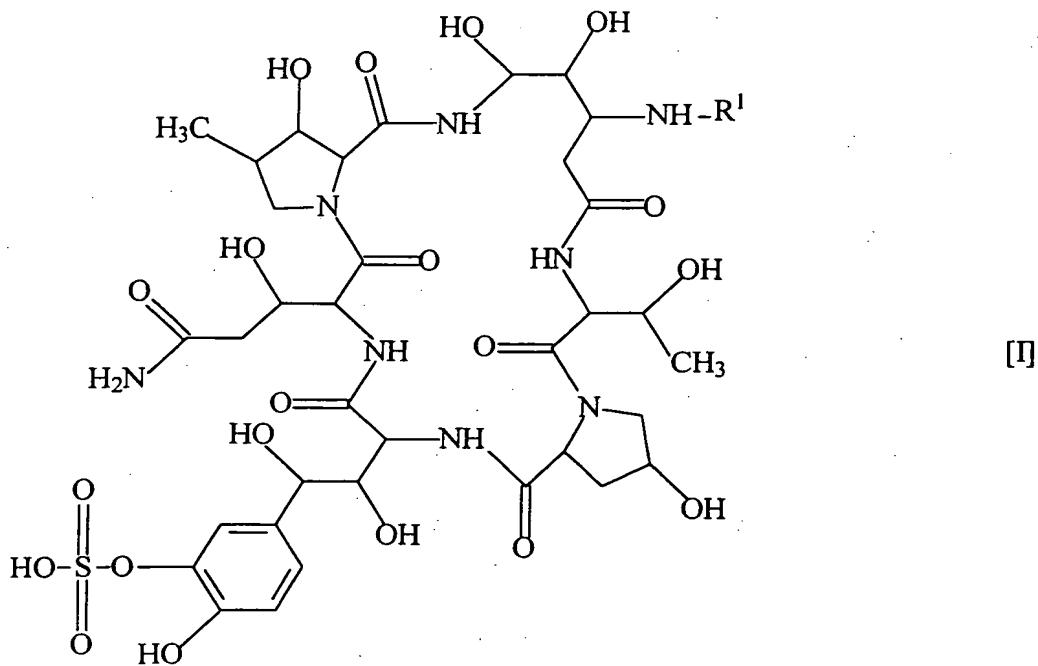
Responsive to the outstanding Office Action issued June 5, 1998, entry of the following amendments and remarks is respectfully requested. The amendment does not raise any new issues and serves to place the application in better form for appeal by reducing or simplifying the issues.

IN THE CLAIMS:

Please cancel Claims 1-16 and 19.

Please add the following new Claims:

--20. A polypeptide compound of the following general formula [I]:



wherein R^1 is selected from the group consisting of:

naphthyl (lower) alkenoyl which may have one or more higher alkoxy;

(C₂-C₆) alkanoyl substituted with naphthyl having higher alkoxy;

ar (C₂-C₆) alkanoyl substituted with aryl having one or more suitable substituent(s),

wherein ar (C₂-C₆)-alkanoyl may have one or more suitable substituent(s);

aryl substituted with a heterocyclic group which may have one or more suitable substituent(s), wherein aryl may have one or more suitable substituent(s); and
a pharmaceutically acceptable salt thereof.

21. A compound of Claim 20, wherein R^1 is selected from the group consisting of:

naphthyl (lower) alkenoyl which may have 1 to 3 higher alkoxy;

ar (C₂-C₆) alkanoyl substituted with aryl having 1 to 3 substituent(s) selected from the

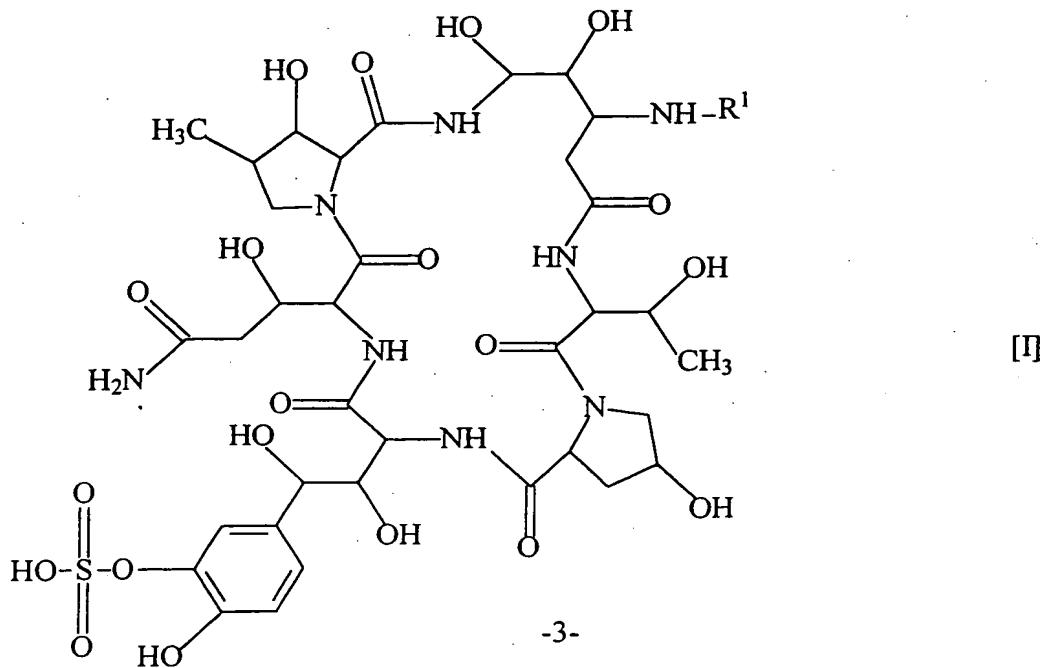
group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy (lower) alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, phenyl having lower alkoxy (lower) alkoxy, and oxo, wherein ar (C₂-C₆)-alkanoyl may have hydroxy, oxo, protected amino or amino; and

(C₂-C₆) alkanoyl substituted with naphthyl having higher alkoxy.

22. A compound of Claim 21, wherein R¹ is selected from the group consisting of: naphthyl (lower) alkenoyl which may have 1 to 3 higher alkoxy; phenyl (C₂-C₆) alkanoyl substituted with phenyl which has 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, and phenyl having lower alkoxy (lower) alkyl, wherein phenyl (C₂-C₆) alkanoyl may have hydroxy, oxo, protected amino or amino; and

(C₂-C₆) alkanoyl substituted with naphthyl having higher alkoxy.

23. A polypeptide having the following general formula [I]:



wherein R¹ is aroyl substituted with a heterocyclic group which may have one or more suitable substituent(s), wherein aroyl may have one or more suitable substituent(s).

24. A compound of Claim 23, wherein R¹ is aroyl substituted with a heterocyclic group which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy (lower) alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, phenyl having lower alkoxy (higher) alkoxy, phenyl having higher alkenyloxy, a heterocyclic group substituted with phenyl having lower alkoxy, a heterocyclic group, cyclo (lower) alkyl having phenyl, phenyl having cyclo (lower) alkyl, phenyl substituted with a heterocyclic group having lower alkyl and oxo, cyclo (lower) alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, and phenyl having a heterocyclic group and oxo, and wherein aroyl may also be substituted with halogen.

25. A compound of Claim 24, wherein R¹ is selected from the group consisting of: benzoyl substituted with a saturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkyl, phenyl having lower alkoxy (higher) alkoxy, phenyl having higher alkenyloxy, piperidyl substituted with phenyl having lower alkoxy, piperidyl, cyclo (lower) alkyl having phenyl, phenyl having cyclo (lower) alkyl, and phenyl substituted with triazolyl having oxo and lower alkyl, wherein benzoyl may also be substituted with halogen; benzoyl substituted with an unsaturated 5-membered heteromonocyclic group

containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy (higher) alkoxy, and phenyl substituted with phenyl having lower alkoxy;

benzoyl substituted with a 5 or 6-membered heteromonocyclic group containing 1 or 2 nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl and phenyl having lower alkoxy; and

benzoyl substituted with a 5-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) and 1 to 2 sulfur atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, cyclo (lower) alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having cyclo (lower) alkyl, phenyl having piperidine, and phenyl having lower alkoxy (higher) alkoxy.

26. The compound of Claim 23, wherein R¹ is selected from the group consisting of: benzoyl substituted with piperazinyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkyl, phenyl having lower alkoxy (higher) alkoxy, phenyl having higher alkenyloxy, piperidyl substituted with phenyl having lower alkoxy, cyclo (lower) alkyl having phenyl, phenyl having cyclo (lower) alkyl, and phenyl substituted with triazolyl having oxo and lower alkyl, and wherein benzoyl may also be substituted with halogen;

benzoyl substituted with isoxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy (higher) alkoxy, and phenyl substituted with phenyl

having lower alkoxy;

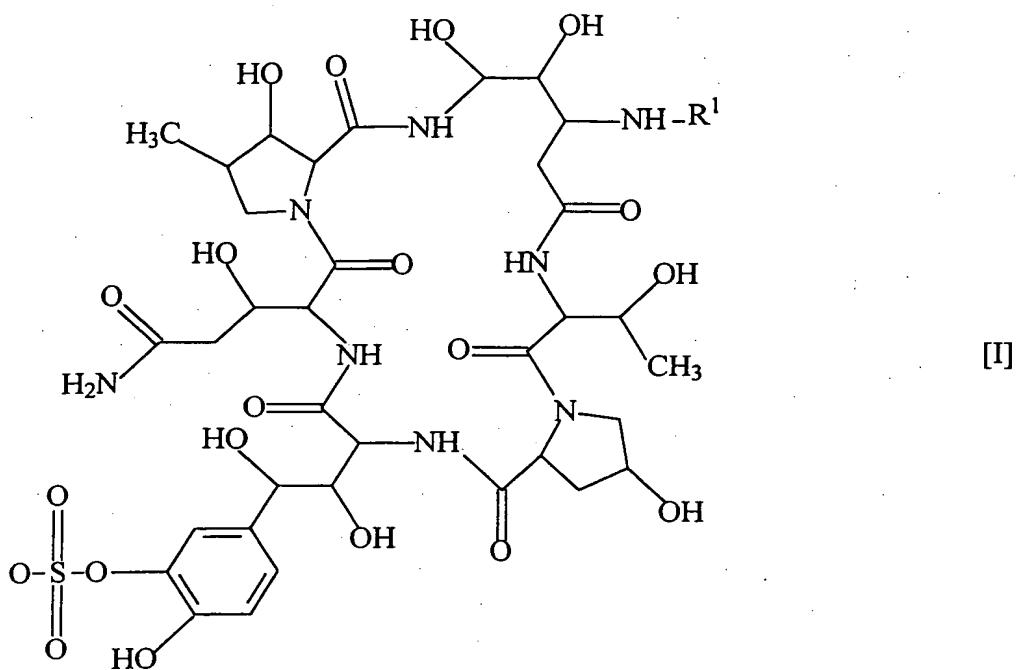
benzoyl substituted with thiadiazolyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, cyclo (lower) alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having cyclo (lower) alkyl, phenyl having piperidyl, and phenyl having lower alkoxy (higher) alkoxy; and

benzoyl substituted with oxadiazolyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy (higher) alkoxy, higher alkyl and phenyl substituted with phenyl having lower alkoxy.

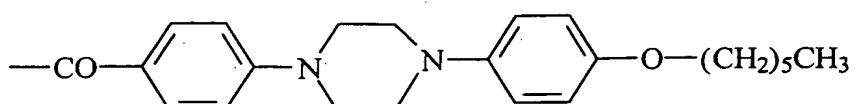
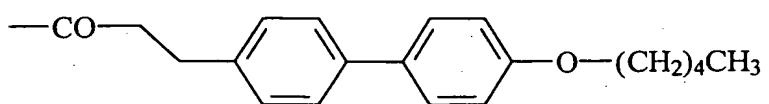
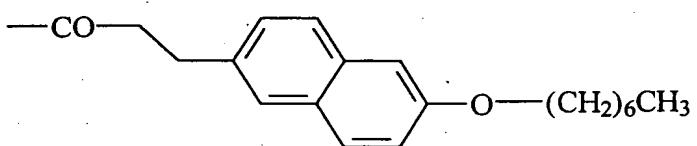
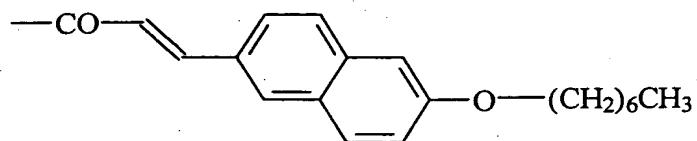
27. A compound of Claim 26, wherein R¹ is selected from the group consisting of:
benzoyl substituted with piperazinyl which may have phenyl having lower alkoxy;
benzoyl substituted with isoxazolyl which may have phenyl having lower alkoxy;
benzoyl substituted with thiadiazolyl which may have phenyl having lower alkoxy (higher) alkoxy; and

benzoyl substituted with oxadiazolyl which may have phenyl having lower alkoxy.

28. A polypeptide compound of the following general formula [I]:

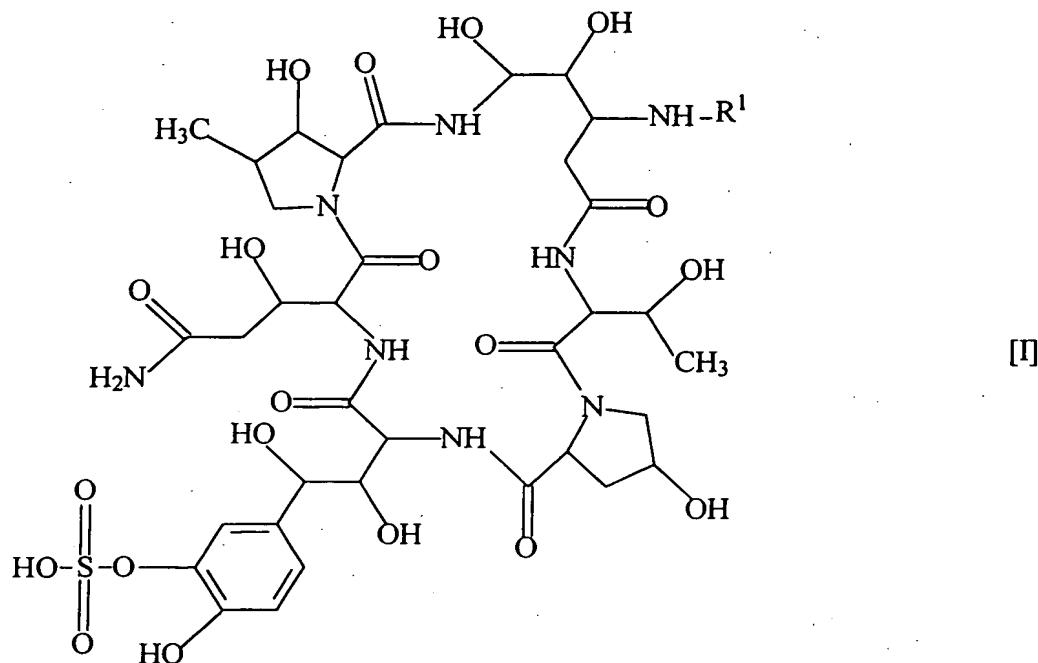


wherein R^1 is selected from the group consisting of:



and a pharmaceutically acceptable salt thereof.

29. A process for the preparation of a polypeptide compound of the formula [I]:



wherein R^1 is selected from the group consisting of:

(C_2-C_6) alkanoyl substituted with naphthyl having higher alkoxy;

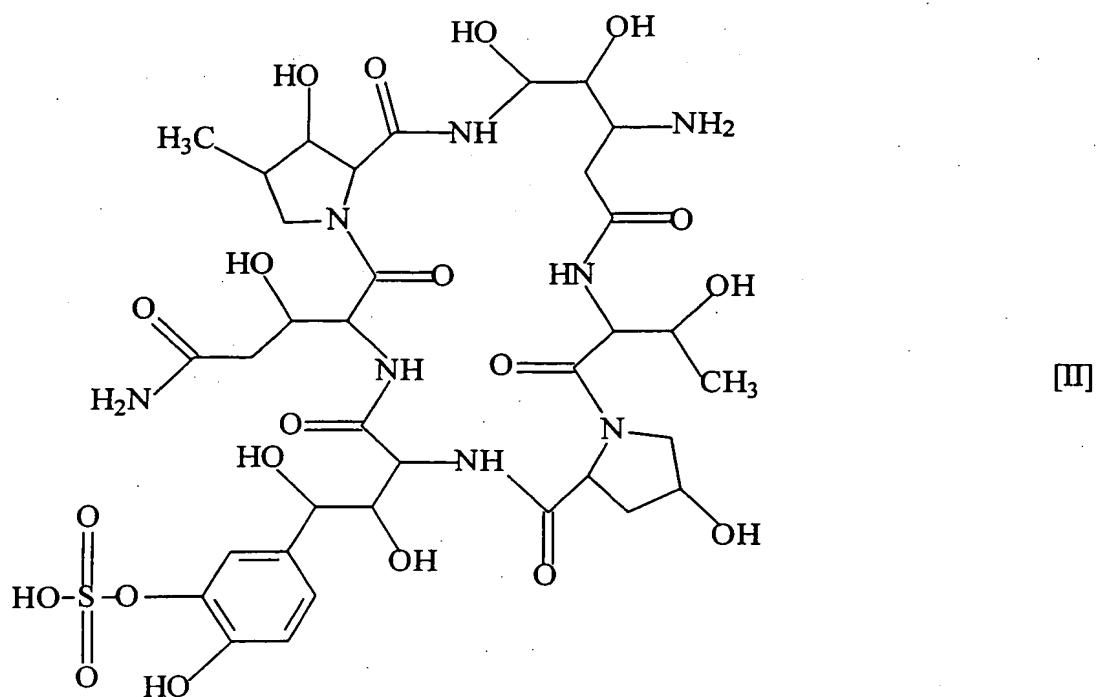
or (C_2-C_6) alkanoyl substituted with aryl having one or more suitable substituent(s),

wherein ar (C_2-C_6) alkanoyl may have one or more suitable substituent(s);

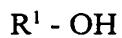
aryloyl substituted with a heterocyclic group which may have one or more suitable substituent(s), in which aryl may have one or more suitable substituent(s); and a pharmaceutically acceptable salt thereof,

which comprises

1) reacting a compound of the formula [II]:



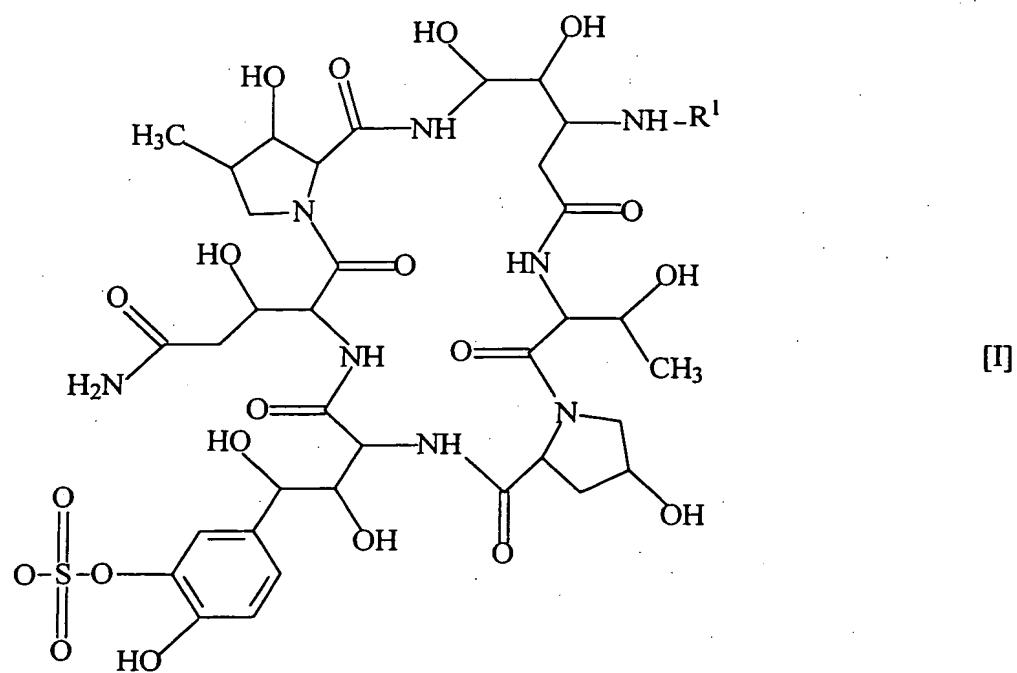
or its reactive derivative at the amino group or a salt thereof, with a compound of the formula [III]:



[III]

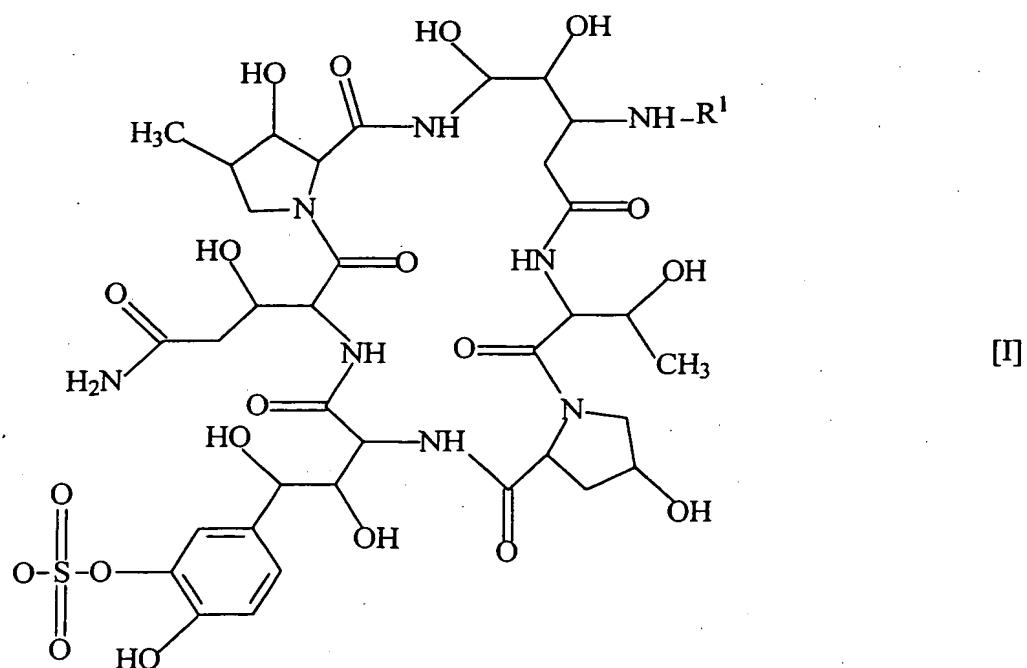
wherein R^1 is defined above,

or its reactive derivative at the carboxy group or a salt thereof, to give a compound [I] of the formula:



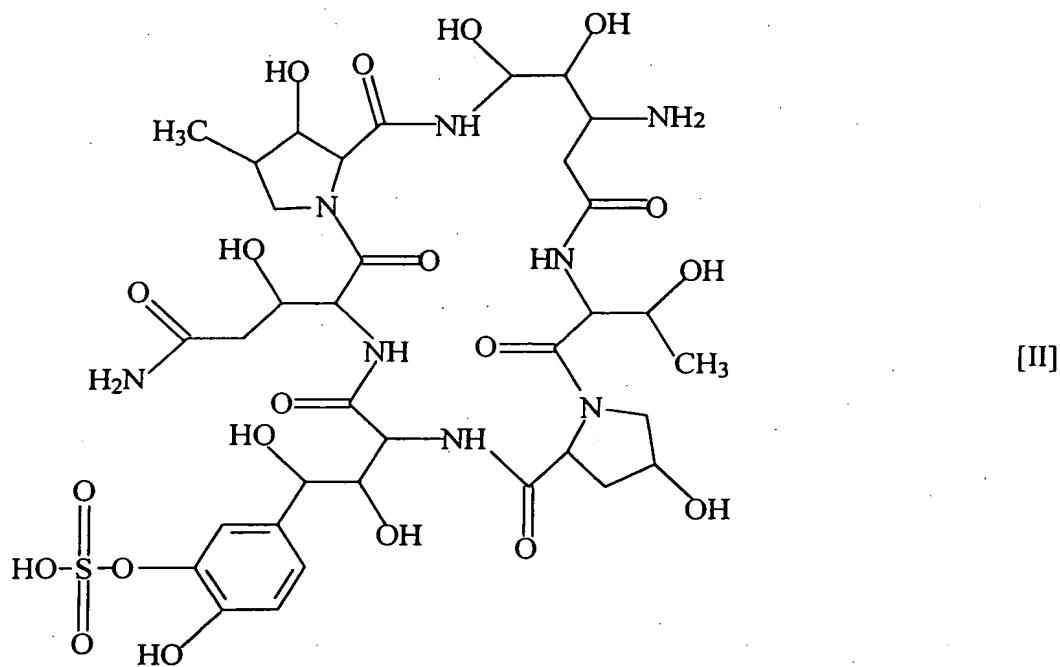
wherein R^1 is defined above, or a salt thereof.

30. A process for the preparation of a polypeptide compound of the formula [I]:



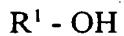
wherein R^1 is aroyl substituted with a heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s) or a pharmaceutically acceptable salt thereof, which comprises

- 1) reacting a compound of the formula [II]:



or its reactive derivative at the amino group or a salt thereof, with a compound of the formula

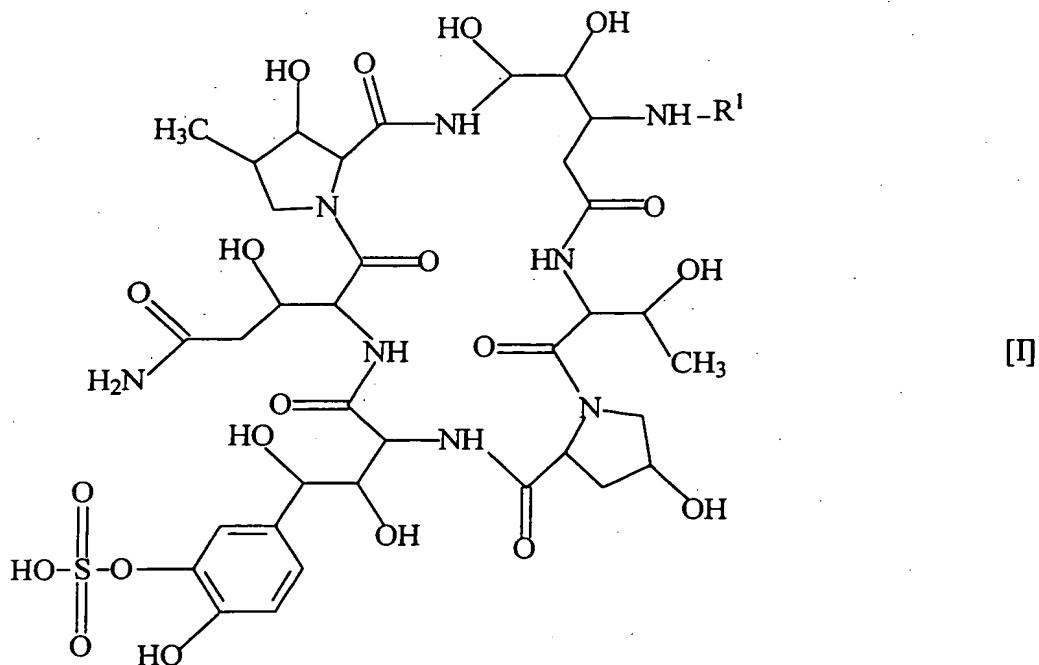
[III]:



[III]

wherein R^1 is defined above,

or its reactive derivative at the carboxy group or a salt thereof, to give a compound [I] of the formula:



wherein R¹ is defined above, or a salt thereof.

31. A pharmaceutical composition which comprises, as an active ingredient, a compound of Claim 20 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers of excipients.

32. A pharmaceutical composition which comprises, as an active ingredient, a compound of Claim 23 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers of excipients.

33. A method for the prophylactic and/or the therapeutic treatment of infectious diseases caused by pathogenic microorganisms which comprises administering a compound of Claim 20 or a pharmaceutically acceptable salt thereof to a human being or an animal.

34. A method for the prophylactic and/or the therapeutic treatment of infectious diseases caused by pathogenic microorganisms which comprises administering a compound

of Claim 23 or a pharmaceutically acceptable salt thereof to a human being or an animal.

35. A pharmaceutical composition which comprises, as an active ingredient, a compound of Claim 28 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers of excipients.

36. A method for the prophylactic and/or the therapeutic treatment of infectious diseases caused by pathogenic microorganisms which comprises administering a compound of Claim 28 or a pharmaceutically acceptable salt thereof to a human being or an animal.--

SUPPORT FOR THE AMENDMENTS

New Claims 20-36 are supported by original Claims 1-16 and 19. Support for Claim 28 can be found on page 17 of the specification as originally filed. No new matter has been added. Claims 20-36 remain active in the case.

REMARKS

Applicants appreciate the interview granted undersigned counsel in the above-captioned application, wherein it was argued that new Claim 20 is commensurate in scope with the showing of superior results using the claimed compounds, presented in the Declaration under 37 C.F.R. §1.132 filed March 2, 1998, since the compounds encompassed by Claim 20 are homologs of the specific compounds tested. The Examiner agreed to give the arguments presented in a request for reconsideration careful consideration. Applicants appreciate the Examiner's acknowledgment that the specific compounds tested showed unexpected results and would be allowable if presented in independent form.

The present invention relates to cyclic hexapeptide compounds having antimicrobial activity in humans and animals, a process for preparing the compounds, a pharmaceutical

composition containing the compound and a method of using the compounds for the prophylactic or therapeutic treatment of infectious diseases.

The rejection of Claims 1-16 and 19 under 103(a) over Toshiro et al. (EP A 0462531) or Toshiro et al. (US Patent 5,376,634) is respectfully traversed.

Since the disclosure of US 5,376,634 appears to be identical to EP 0 462 531, the following discussion applies to both references.

Toshiro et al. does not disclose Applicant's cyclic hexapeptide. The R₁ substituent on the compounds of Toshiro et al. may be either hydrogen or acyl, whereas in the presently claimed compounds it must be acyl. Toshiro et al. disclose that suitable acyl groups are those listed at column 6, line 30 through column 8, line 5. This encompasses hundreds of compounds. However, none of the acyl groups described is an aroyl substituted with a heterocyclic group, as recited in Claim 23 of the instant application. The only description of R₁ being an aroyl group is at column 7, line 44, but there is no description of the aroyl group being substituted with a heterocyclic group. Nor are there any examples in Toshiro et al. of compounds wherein the R₁ is aroyl substituted with a heterocyclic group. Therefore it is respectfully submitted that independent Claims 23 and 30, wherein R₁ is aroyl substituted with a heterocyclic group and Claims 24-27, 32 and 34, dependent therefrom, are all patentable over Toshiro et al.

Applicants have shown, via the Declaration filed March 2, 1998, the superiority of the presently claimed compounds compared to two of the preferred compounds in Toshiro et al. The Examiner agreed that a claim to those specific compounds would be allowable if presented. Therefore, Applicants have presented Claim 28, which is drawn to examples 16, 20, 21 and 23 from the specification which were shown in the Declaration to have superior

antifungal properties compared to two of the preferred compounds in Toshiro et al.

Therefore, Claim 28 and Claims 35 and 36, dependent therefrom are submitted to be patentable over Toshiro et al.

Claim 20 has been limited to four choices for R¹ which are submitted to be representative of the compounds of Examples 16, 20, 21 and 23, shown to have superior antifungal activity. Specifically, R¹ may be: naphthyl(lower)alkenoyl which may have one or more higher alkoxy, which is representative of the compound of Example 21 in which R¹ is naphthyl-C₂-alkenoyl having a C₇-alkoxy group; (C₂-C₆) alkanoyl substituted with naphthyl having higher alkoxy, which is representative of the compound of Example 20 in which R¹ is C₂ alkanoyl substituted with naphthyl having a C₇ alkoxy group; ar(C₂-C₆) alkanoyl substituted with aryl having one or more suitable substituents, which is representative of the compound of Example 16 in which R¹ is phenyl-C₂-alkanoyl substituted with phenyl having C₇ alkoxy; and aroyl substituted with a heterocyclic group which may have one or more suitable substituents, which is representative of the compound of Example 23 in which R¹ is phenoyl substituted with piperazinyl which is substituted with phenyl having a C₆ alkoxy group. The above-described R¹ groups should be considered to be representative of the specific compounds shown in the Declaration since they are homologs, i.e., a family of related compounds, the composition of which varies from member to member by a CH₂ group. Chemists knowing the properties of one member would in general know what to expect in adjacent members. Objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support. By the same token, Applicant is not required to test each and every species within the scope of the claims. Rather, patentability is established by a showing of unexpected superiority for representative

compounds within the scope of the claims. Ex parte Winters, 11 USPQ2d 1387 (Bd. Pat. App. & Int. 1988). Applicants submit that the compounds tested are representative of the scope of the compounds recited in Claim 20 since they are homologs. Therefore, it is respectfully requested that the rejection be withdrawn.

The rejection of Claims 1-19 under the judicially created doctrine of obviousness-type double patenting over the claims of U.S. Patent 5,374,634, to Toshiro et al., is respectfully traversed.

This rejection is traversed based on the showing of unexpectedly superior antifungal properties of the claimed compounds. Additionally, this rejection is improper for Claims 23 and 30 and Claims 24-27, 32 and 34, since there is no disclosure or suggestion that R₁ is an aroyl substituted with a heterocyclic group in the specification or the claims of Toshiro et al. Therefore, it is respectfully requested that this rejection be withdrawn.

Applicants submit that the application is now in condition for allowance, and an early notification of such action is earnestly solicited.

Respectfully submitted,

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18-0971-0 PCT



IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF

HIDENORI OHKI ET AL

: EXAMINER: MARSHALL

SERIAL NO: 08/809,723

: GROUP ART UNIT: 1654

FILED: MAY 21, 1997

: GROUP ART UNIT: 1654

FOR: CYCLIC HEXAPEPTIDES

HAVING ANTIBIOTIC ACTIVITY

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

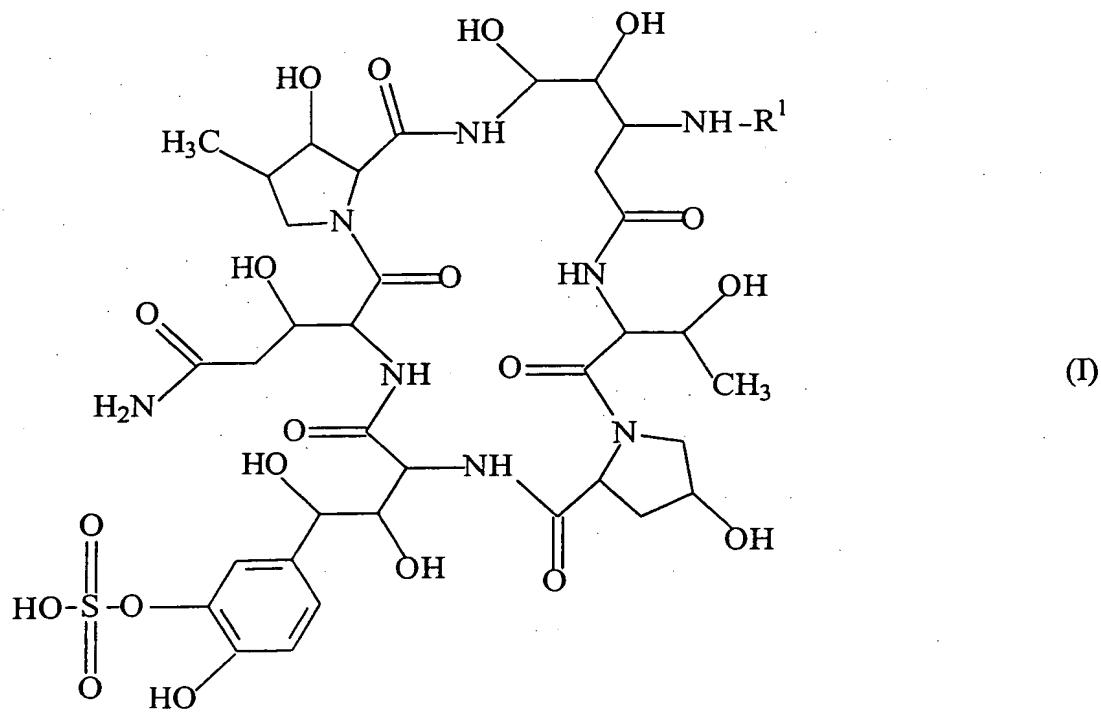
SIR:

Prior to examination please amend the above-identified application as follows:

IN THE CLAIMS

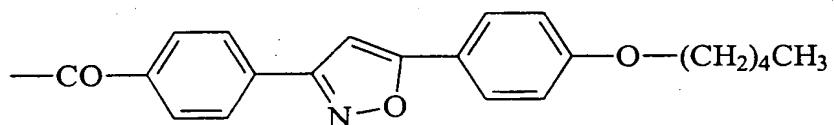
Cancel claims 20-36. Please add the following new claims:

--37. A polypeptide compound of the following general formula (I):

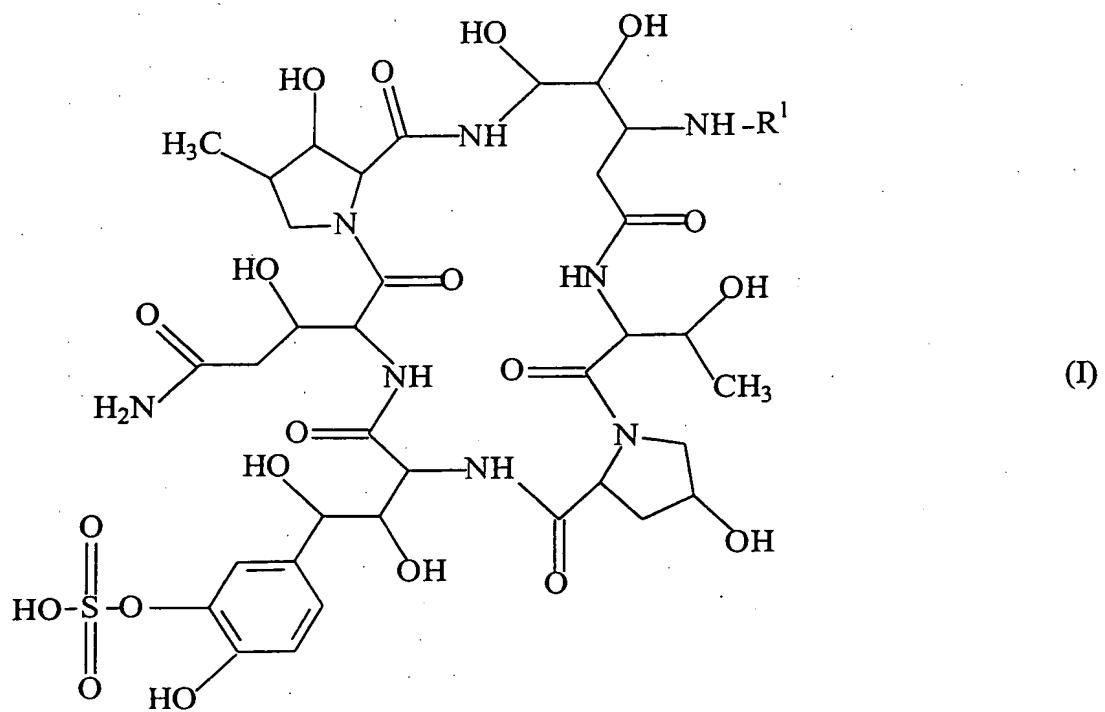


wherein R^1 is benzoyl substituted with isoxazolyl which has phenyl having lower alkoxy, or a salt thereof.

38. A compound of claim 37, wherein R^1 is

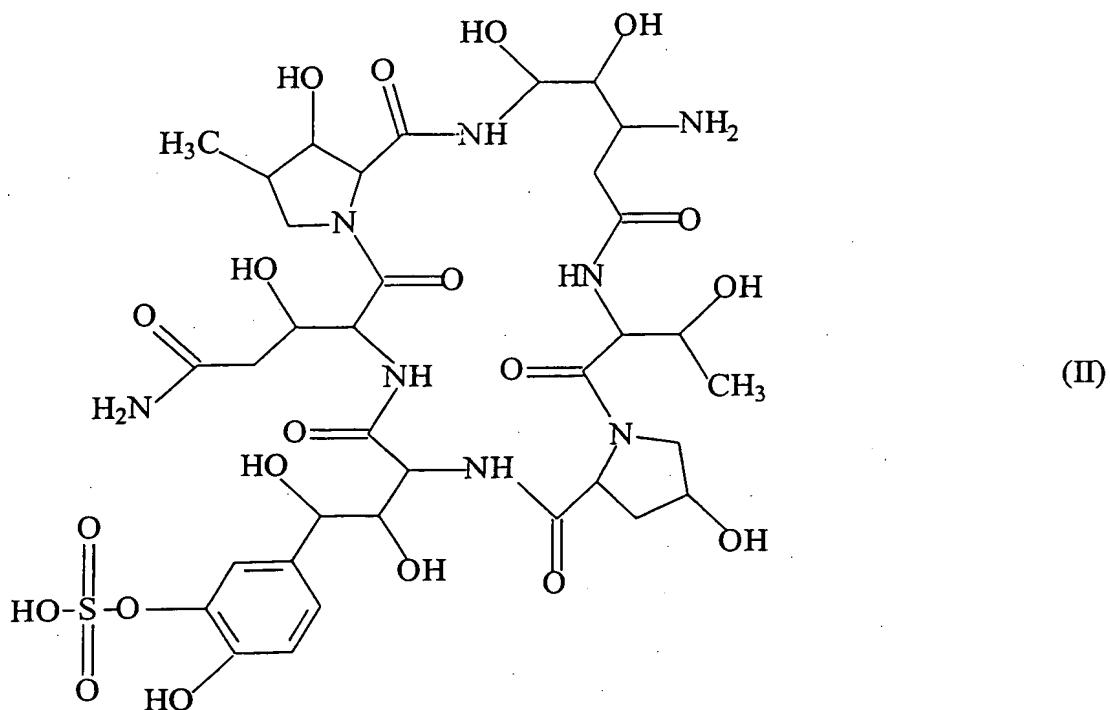


39. A process for the preparation of a polypeptide compound of the formula (I):



wherein R^1 is benzoyl substituted with isoxazolyl which has phenyl having lower alkoxy, or a salt thereof, said process comprising:

- 1) reacting a compound of the formula (II):



or its reactive derivative at the amino group or a salt thereof, with a compound of formula

(III):



or its reactive derivative at the carboxy group or a salt thereof, wherein R^1 is defined above, to give a compound of formula (I).

40. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 37, or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or excipient.

41. A method for the therapeutic treatment of infectious diseases caused by pathogenic microorganisms, comprising administering an effective amount of a compound of claim 37 or a pharmaceutically acceptable salt thereof, to a human being or animal.--

REMARKS

Claims 37-41 are active in the application.

This case is a CPA of application serial No. 08/089723, in which a declaration was filed pursuant to 37 C.F.R. §1.132. The major issue in that case concerned whether the claims were commensurate in scope with data showing superior antifungal properties. The present claims are narrower, being directed to compounds in which R¹ is benzoyl substituted with a heterocycle which is itself substituted by phenyl having an alkoxy substituent. These claims are commensurate in scope with data in the previously filed Rule 132 Declaration and the one submitted herewith (unexecuted) with data on the compound of Example 25 (claim 38).

Applicants submit that the case is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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